REMARKS

Claims 171-188 and 205-286 have been canceled without prejudice. Applicants maintain the right to prosecute the subject matter of any canceled claim in one or more related applications. New claims 287 to 345 have been added to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amendments and new claims can be found in the specification of the present application, for example as outlined in the following table:

Claims	Support in the Specification
287	Page 15, lines 30-34
288	Page 33, lines 5-30
289	Page 14, line 7
290-293	Page 7, lines 3-8; Figs. 3A-3D
294	Page 15, line 21
295-296	Page 64, line 1 to page 67, line 19
297-306	Page 19, lines 22-35
307-311	Page 18, line 26 to page 19, line 4
312	Page 16, lines 14-18
313	Page 15, lines 3-4
314-317	Page 14, lines 7-11
318	Page 18, lines 13-25
319	Page 41, lines 22-25
320-324	Page 32, line 9 to page 33, line 4
325	Page 35, lines 20-22; page 36, line 32 to page 37, line 1
326	Page 37, lines 2-18
327	Page 14, line 7
328-329	Page 21, lines 17-25; page 22, lines 20-30
330-335	Page 14, line 7; page 16, lines 24-27; page 64, line 1 to page 76, line 19
336	Page 16, lines 14-18
337-345	Page 7, lines 3-8; Figs. 3A-3D; page 14, lines 7-15; page 15, lines 21-34; page 35, lines 20-22; page 36, line 32 to page 37, line 18; page 41, lines 22-25; page 64, line 1 to page 67, line 19

No new matter has been added.

Upon entry of the amendments made herein, claims 287 to 345 will be pending in the present application.

INTERVIEW SUMMARY RECORD

Applicants and Applicants' representatives thank Primary Examiner Phillip Gambel for the courtesy of the recent interview in connection with the above-identified application. The interview was conducted on September 9, 2003 ("the Interview") between Examiner Gambel and Applicant Dr. David Cheresh, Applicants' representative, Dr. Thomas Fitting, and attorneys Margaret B. Brivanlou and Jonathan Klein-Evans on behalf of the licensee of the above-identified application in connection with the above-referenced application. During the Interview, the outstanding Office Action was discussed, in particular the rejection of claims 171-188, and 205-286 under 35 U.S.C. §103(a).

Applicants and Applicants' representatives discussed with Examiner Gambel why the claimed invention cannot be rendered obvious by the references of record cited by the Examiner. In particular, Dr. Cheresh discussed the Cheresh (WO 89/05155) reference -- cited by the Examiner as a primary reference and the only reference cited by the Examiner that actually provides *in vivo* results from administration of an anti-$\alpha_v\beta_3$ antibody -- specifically in a mouse model. Dr. Cheresh explained to the Examiner that LM609, the anti-$\alpha_v\beta_3$ antibody used to demonstrate anti-tumor activity in the mouse model, does not and cannot react with murine blood vessels. Specifically, LM609 is a murine antibody that was raised against human $\alpha_V\beta_3$ and does not recognize murine $\alpha_V\beta_3$ (*see, e.g.,* Brooks et al., J. Clin. Invest., 96:1815-22, 1995). Thus, LM609 cannot bind and directly have an effect on murine cells. The only human cells in the mouse model disclosed in the Cheresh reference are the melanoma tumor cells. As such, any tumor growth inhibiting activity reported in the Cheresh reference is necessarily derived from LM609 (the anti-$\alpha_v\beta_3$ antibody used) interacting with the tumor cells because the only cells in the mouse model capable of interacting with LM609 are the human tumor cells. LM609 does not react with murine blood vessels and, thus, any tumor growth inhibiting effect observed was not due to inhibition of angiogenesis.

Applicants and Applicants' representatives explained why a *prima facie* case of obviousness was not made by the Examiner because since (i) the cited references fail to suggest all of the limitations of the claimed invention; (ii) the cited references fail to provide the legally required "reasonable expectation of success"; (iii) there would have been no motivation to combine the secondary references with the primary references and with each other; and (iv) even if combined, the secondary references cited by the Examiner actually teach away from the claimed invention.

Moreover, Dr. Cheresh explained to the Examiner that the data in the instant application demonstrate that administration of anti-$\alpha_v\beta_3$ antibodies to a tumor in a system in which the antibody reacts with the blood vessels results surprisingly in tumor regression. In contrast, Dr. Cheresh explained that in the Cheresh reference, administration of LM609 intraperitoneally to

mice having human melanoma tumor grafts results in inhibition of tumor graft growth rates as compared to controls (Cheresh at pages 47-48), *i.e.*, the tumors still grew in the presence of LM609, albeit more slowly. In sum, the Cheresh reference reports that tumor growth rates were slower when treated with LM609 than with control; however, the methods of the instant invention result in tumor regression. Indeed, when these results were first reported, lay media and angiogenesis experts such as Dr. Judah Folkman who did pioneering tumor angiogenesis studies recognized that these results were unprecedented. Applicants' representatives showed the Examiner a New York Times article quoting Dr. Folkman as saying, "no one had thought that you could get tumor regression" in response to reports of Applicants' results. For the Examiner's convenience, attached herewith is a copy of the article. Without conceding that the Examiner has made a *prima facie* case of obviousness, Applicants' representatives submitted that these unexpected results would rebut the obviousness rejection maintained by the Examiner.

The Examiner and Applicants' representatives also discussed the submission of claims directed to methods of inducing tumor tissue regression which Examiner Gambel indicated he would consider and should be allowable over any cited references of record in the instant application (*see* Interview Summary Record, dated September 9, 2003). Dr. Cheresh and Applicants' representatives also brought to the Examiner's attention clinical trials involving Vitaxin -- a humanized version of LM609. In particular, Dr. Cheresh discussed the results of a Phase I study evaluating the safety and pharmacokinetics of Vitaxin in humans with cancer. Of the 17 patients treated, 14 were evaluated. The treatment was well tolerated with little or no toxicity. Over 6 weeks of therapy, one patient demonstrated a partial response, and seven patients demonstrated stable disease. The publication reporting the results of this clinical study is included in the Supplemental Information Disclosure Statement submitted concurrently herewith. *See* Gutheil et al. (Clin. Cancer Research, 6: 3056-3061, 2000).

THE REJECTION UNDER 35 U.S.C. §103(a) SHOULD BE WITHDRAWN

The Examiner has maintained the rejection of claims 171-188, and 205-286 under 35 U.S.C. §103(a) as being obvious over Kim (WO 93/20229) and/or Cheresh (WO 89/05155) in view of Nicosia et al. (Am. J. Pathol., 138:829-833, 1991; "Nicosia"), Nip et al. (J. Clin. Invest., 90:1406-1413, 1992; "Nip")[1], Folkman et al., (Seminars in Cancer Biology, 3:89-96, 1992;

[1] Applicants take the opportunity to clarify a comment in the response filed November 26, 2002 in which Applicants indicated that Nip reports that the incidence and growth rate of primary tumors were unaffected by treatment with anti-$\alpha_V\beta_3$ antibodies (*see* Response at pages 7-8). More precisely, Nip suggests that the incidence and growth rate of primary tumors would not be affected by treatment with anti-$\alpha_V\beta_3$ antibodies. Nip reports comparative data showing that the incidence and growth rate of primary tumors in tumor bearing mice were not

"Folkman"), Pignatelli et al. (Hum. Pathol., 23:1159-1166, 1992; "Pignatelli") and art known procedures of treating cancers of interest at the time the invention was made.

Applicants respectfully disagree and submit that the Examiner has failed to establish a *prima facie* case of obviousness because the primary references do not teach all of the limitations of the claims and the secondary references do not cure the defects of the primary references, and in fact, on balance, teach away from the claimed invention. Moreover, the surprising results of obtaining tumor regression by administration of anti-$\alpha_v\beta_3$ antibody, as discussed above in the interview summary, would overcome any *prima facie* case of obviousness that could be made out. However, to expedite prosecution, Applicants have canceled claims 171-188 and 205-286, without prejudice, in favor of pursuing new claims 287 to 345. New claims 287 to 345 have been added to more particularly point out and distinctly claim that which Applicants regard as the invention. As discussed above, the Examiner indicated such claims would be considered favorably. Accordingly, Applicants respectfully submit that the instant rejection has been rendered moot and should be withdrawn.

Summary

Applicants believe that a complete response is provided in the foregoing remarks to each issue and grounds for rejection and objection raised by the Examiner. Applicants submit that patentable subject matter exists with regard to the pending claims and therefore respectfully requests favorable action and entry of the present Response. The application is now believed to be in proper condition for allowance and early notification of allowance is earnestly solicited. The Examiner is invited to telephone the undersigned if it would be deemed helpful to advance the application.

Respectfully submitted,

September 16, 2003

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significantly different when innoculated with recombinant tumor cells having various $\alpha_V\beta_3$ receptor expression levels (*see* Nip p. 1408, left col.), suggesting that treatment with anti-$\alpha_V\beta_3$ antibodies would also not affect incidence and growth rate of primary tumors.